FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 14, ISSUE 2 ■ MARCH–APRIL 2006

Marriage of the Minds
CO-EQUALS CO-CHAIR INHERITED DISEASE RESEARCH BRANCH

by Karen Ross

Karen Ross

Branch Mates: *Alexander Wilson and Joan Bailey-Wilson, co-chiefs of the Inherited Disease Research Branch, NHGRI, at Baltimore's Bayview campus. She heads the Statistical Genetics Section, and he heads the Genometrics Section.*

Alexander Wilson and his wife Joan Bailey-Wilson have two families: their two children at home and the 20-odd students, postdocs, and research staff who make up the Inherited Disease Research Branch (IDRB) at NHGRI.

The pair, who were recently named co-chiefs of the IDRB, use statistical methods to tease out which genes contribute to complex disorders such as cancer and depression.

So far, one of the most challenging aspects of their new position has been coping with the attention that their status as married co-chiefs has brought. In addition to this article, the *Baltimore Sun* featured Wilson and Bailey-Wilson in its Health and Science section, just before Valentine's Day, where the couple's story shared space with a large photograph of a chocolate bar.

For the junior scientists in the group, it was an irresistible opportunity to poke fun at their leaders.

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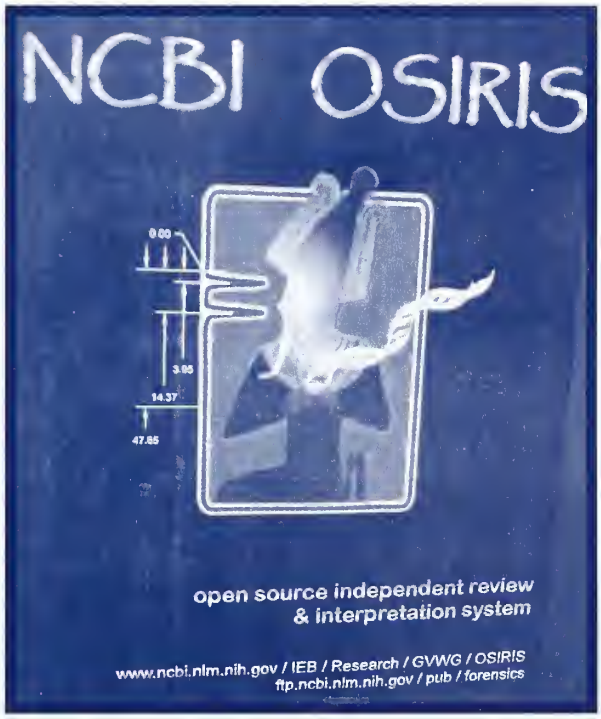
NIH WTC Team Reactivated in Hurricanes' Wake
FORENSICS MEETS MEDICAL GENETICS IN MASS FATALITY VICTIM IDENTIFICATION

by Fran Pollner

The members of the NIH team who had worked together for nearly four years to assist in the identification of victims of the September 2001 World Trade Center (WTC) disaster were again called into action in the wakes of Hurricanes Katrina and Rita.

It was only a few months after the last official meeting in June 2005 of the WTC Kinship and Data Analysis Panel (KADAP) that the calls started going out to reactivate the group. Their experience and expertise were needed to meet the similar—and also quite different—challenges of identifying the Gulf Coast victims.

"It was thought that we could hit the ground running—and, actually, we did," Joan Bailey-Wilson said, referring to the seasoned NHGRI-NCBI cohort whose base of local victim-identification operations, when they are away from NIH, has moved from New York City to Baton Rouge, La.



Egyptian God of the Dead, OSIRIS *offers an apt acronym for the "semiautonomous" software program developed by NCBI's Steve Sherry and his team to verify rapidly the quality of DNA data — "thousands of records in seconds, tens of thousands in minutes"—and spotlight those findings (perhaps 10 percent) whose ambiguity warrants and can only be resolved by human judgment*

From KADAP to HVDIEG

The lessons learned in the former effort are being adapted to the unique circumstances of the latter; an approach to identifying victims of mass fatalities in general is emerging; and, increasingly, advances in the science of forensic DNA identification are serving to advance the science of medical genetics—and vice versa, say the NIH investigators.

Among the original members of the KADAP and now a part of the Hurri-

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First Steps to an Intramural Roadmap

Michael Gottesman

Elias Zerhouni

Because the intramural program provides an ideal environment for the conduct of high-risk, high-impact research, it makes sense to think about ways in which intramural scientists can work together to attack problems that cannot easily be solved elsewhere. This perspective is the heart of the NIH Roadmap.

Nonetheless, we have heard talk from many an intramural scientist that our intramural research program has been less involved in the current NIH Roadmap initiative (see <**http://www.nihroadmap.nih.gov**>) than seems warranted. And they wonder why.

Although several Roadmap projects do involve the intramural program—including the imaging probe development center, the high-throughput chemical library screening facilities, the RAID expansion program for preclinical drug development, enhancement of the Clinical Research Training Program, and interdisciplinary training activities—most of the Roadmap activities, in fact, have been focused on extramural scientists.

The goals of the original NIH Roadmap were to identify specific science areas that needed support in order to accelerate progress in generating new tools for basic laboratory investigation, clinical research, and training. These specific programs were developed after substantial input from both extramural and intramural scientists and were intended to provide broad-based support for research activities that would enhance research programs in all of our Institutes and Centers.

Initially, we encouraged the intramural program to think of ways to complement some of the Roadmap activities, and many of our scientists have taken up the challenge to develop new highways and byways to accomplish goals similar to those defined in the original Roadmap.

It is time now to expand these explorations to create new scientific frontiers.

In thinking about how an intramural Roadmap can best contribute to the overall biomedical research effort, it is clear that we must take full advantage of the resources and talent we have and forge entirely new directions that can revolutionize research and clinical applications.

We will start with a series of focus groups involving intramural and extramural scientists who are eager to think creatively about current research challenges and how best to utilize the special resources at NIH to address them. The product of their effort will be a series of initiatives that will garner trans-NIH support and ignite new synergies among intramural scientists.

The greater the number of intramural scientists and scientific leaders involved in this activity, the more likely its success. So, please, take up this challenge and send us your ideas.

—Michael Gottesman
Deputy Director for Intramural Research
—Elias Zerhouni
Director, NIH

Cast Call

In response to Michael Gottesman's editorial in the January-February 2006 NIH Catalyst, *"Finding Ways to Cast a Wider Net":*

To the Editor,

A grass-roots organization of tenure-track and tenured faculty is forming as a trans-NIH initiative with the endorsement of the DDIR to aid in the recruitment of new faculty to NIH.

The Recruitment Group will work together with search committees after a candidate has been identified. Volunteers will meet informally to address a candidate's specific scientific or personal issues, and discuss the unique benefits of research at NIH.

The idea is to provide a personal and friendly introduction to NIH and match job candidates with similar faculty who are thriving in intramural NIH. We also plan to create a website to provide information about housing, schools, and other aspects of life at NIH specifically directed at the questions frequently asked by job applicants.

At the moment we are looking for two types of volunteers: 1) those who'd like to be on the executive committee and help develop the idea and manage it and 2) those who would prefer not to be on the committee but would rather serve as a faculty contact willing to talk to and meet with top candidates to tell them about your experiences.

If you are interested in either capacity in helping in the future recruitment of outstanding faculty candidates to NIH, please contact:

Julie Segre, 301-402-2314,
<**jsegre@mail.nih.gov**>,
or Mike Lenardo, 301-496-6754,
<**lenardo@nih.gov**>.

A Farewell to NIH . . .

Celia Hooper, who has been the Scientific Editor of The NIH Catalyst *since its inception, separated from NIH on March 31, 2006, in pursuit of new horizons. With this poem, she left her best wishes and fond farewells to NIH friends and colleagues, and claimed great pride to have worked with these amazing people, with NIH, and with* The Catalyst *for more than 13 years.*

Apoptotic Adiós

It's so easy to miss when you lose yourself
in bleeding bureaucracy, budget headaches,
death by a thousand papercuts...
Maybe it fell through the cracks among interesting conflicts,
or its endlessly-circling-hell,
desperate for parking.
Perhaps expired I.D. left it mummified
in a peripheral pedestrian security cage
(PPSC) off Battery Lane.

But it's probably still alive someplace here,
so I frisk the grounds; peruse the faces;
look in the labs; scour the clinics and wards;
feel once more for a pulse.
Not asking, just feeling one last time
for the poetry of the place.

Working late, a colleague calls — Look at that Moon!
I look out, as the Worm Moon floods the grounds.
And later, heading home, pass a wild spring mix
of thoughtful faces. Late night labwork —
the ultimate melting pot. Some will keep digging
all night for illumination.

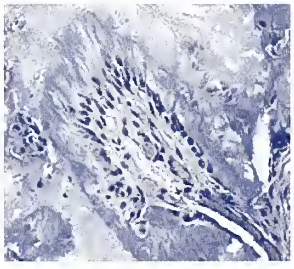
And sure enough, in some lab,
peering in yet another section,
she finally sees it! How it works!
She holds the moment tenderly as a newborn,
humbled and exalted,
first witness to a tiny face of Creation.

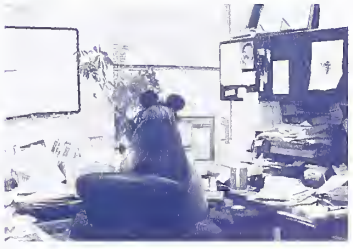
Next morning I'm back,
¡Hola! (The cleaning lady tutors my Spanish.)
I pass through the waiting room:
faces of faith — here for a dip
in the current-swirl of science,
their "last best hope." Perhaps today
the angel of insight
will swoop down, troubling the pool
of knowledge
to heal against all odds
through this awkward lab-coated agent.
Or, to translate:
Sometimes when Bethesda's moon is just so,
the membrane between spirit and science
grows riddled with rafts of traversing protein filaments —
hope, discovery, compassion, creation, insight.

So when I say Adiós, and walk away for good,
I'll try not to squish the worms. I know
somehow, as with the death of my beloved,
tears and years will gently debride
the grief, and leave behind
the poetry of the place.

— Celia Hooper —

— 30 —





Co-equals Co-chair
NHGRI Research Branch

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Karen Ross

A team on the homefront and the workfront, Alexander Wilson and Joan Bailey-Wilson enjoy what they believe is a unique arrangement, co-chairing a NHGRI research branch dedicated to uncovering the genetic and environmental components of inherited diseases

Professionally, Wilson and Bailey-Wilson have different, but complementary, interests. Both of them examine family and population data to find patterns in the transmission of thousands of markers, small regions of DNA sequence that are scattered throughout the genome.

"The markers are our little signposts along the sequence," says Bailey-Wilson. When a marker shows up more often in individuals with a particular disease, a gene that lies near that marker is likely to contribute to that disease.

Some diseases—cystic fibrosis, for example—are caused by defects in a single gene, and the causation between the gene and the disease is very clear.

The diseases that Wilson and Bailey-Wilson study, however, are probably caused by a confluence of many genes, and the effect of any one gene may be quite modest.

Therefore, they rely on sophisticated statistical methods and heavy computer power. To get the large sample sizes they need, they collaborate with investigators from institutions around the world.

'Qualitative' Lung Cancer, 'Quantitative' Depression

Their work diverges when it comes to the diseases they study. Wilson jokes, "Joan and I divided the world a long time ago into qualitative disease and quantitative traits."

Bailey-Wilson focuses on diseases such as cancer for which the diagnosis is qualitative—the patient is either affected or unaffected. Wilson studies diseases such as depression that have quantitative measures of severity and response to treatment.

One of Bailey-Wilson's main interests is lung cancer, a disease that appears to have a fascinating tangle of genetic and environmental causes. "We know smoking is the most important risk factor," she says.

However, some families have disproportionately high rates of lung cancer even after smoking is taken into account, strongly suggesting a genetic contribution. "It may be a genetic risk where you need the smoking to see the risk due to the gene," she says.

She and her collaborators have recently identified a region of the genome that is linked to a high incidence of lung cancer. The region contains hundreds of genes, so they are now doing a finer-scale analysis to figure out which gene is the culprit.

Bailey-Wilson hopes that giving affected families the knowledge that they are high risk "will be the motivation needed to keep young people from starting to smoke and that extra motivation needed to help people quit."

In addition to her lung cancer work, Bailey-Wilson is also investigating the genetic basis of several other types of cancer and other disorders, including nearsightedness.

Before You Know It . . . .

In collaboration with Francis McMahon and other investigators at NIMH and at the University of Texas Southwest Medical Center at Dallas, one of Wilson's projects has recently led to the discovery of a marker in the 5HTR2A serotonin receptor on chromosome 13 that affects how well depressed patients respond to a particular antidepressant medication.

"Fifteen years ago I wrote a paper reporting a linkage between depression spectrum disease and the esterase D [ESD] marker on chromosome 13 and noted that the 5HTR2A receptor was quite close to the ESD marker. Fifteen years later, we find an association with a marker in the 5HTR2A gene and replicate it—twice," says Wilson.

He is also pursuing projects with two sets of collaborators at the Johns Hopkins University School of Medicine in Baltimore—one on the effects of low-dose aspirin therapy on circulatory system disease and the other on scoliosis.

Neither Wilson nor Bailey-Wilson can really say what effect the overlap in their personal and professional lives has had on their careers or their family. It's hard to say, says Wilson, because they have no basis for comparison. "This is what we do; it's not what we chose to do; it's just what we do," he says. Besides, if they ever did things differently, they "would have to do it 100 times" to get good statistics, he continues.

Bailey-Wilson notes that it is nice to have a colleague at home to talk to but that the kids can get bored when the dinner conversation turns to technical genetics issues.

At work, she says, they are neither competitors nor collaborators, but their accomplishments are "mutually beneficial." As Wilson puts it, their individual progress "is good for the branch, and because we are married, it's not only good for the branch, it's good for us." ■

Bisecting Bios

The personal and professional relationship of NHGRI's husband-and-wife researchers Alexander Wilson and Joan Bailey-Wilson spans more than three decades.

They met as undergraduates while working with the sole genetics faculty member at Western Maryland College (now called McDaniel College), a small liberal arts college in Westminster, Md. One thing led to another, and they ended up attending graduate school together at Indiana University, where they studied medical genetics sprinkled with a healthy dose of mathematics and computer science.

They were married in 1978, and two years later they received their doctorates and went to Louisiana State University Medical School in New Orleans to work with Robert Elston. Elston is one of the leading figures in statistical genetics, a then-emerging field that draws on elements of epidemiology, genetics, molecular biology, computer science, and statistics. They entered LSU as postdoctoral fellows and stayed for 15 years, each ultimately reaching the rank of full professor.

When Elston left LSU for Case Western Reserve University in Cleveland in 1995, Wilson and Bailey-Wilson decided to relocate as well—to NHGRI.

Initially they were in separate branches—Wilson in the Genetic Disease Research Branch led by Robert Nussbaum and Bailey-Wilson in the Medical Genetics Branch led at the time by Clair Francomano. However, their work was so different from that of the other more traditional bench scientists in their branches that they posed an administrative challenge.

"We don't purchase supplies; we make contracts for data collection. When we buy computers, it's not laptop computers, it's big servers," explains Wilson.

So two years later, Wilson and Bailey-Wilson became a branch unto themselves—the IDRB. Because NIH's anti-nepotism rules prohibit one spouse from supervising the other, Nussbaum was appointed acting chief of the branch. Over the years, Nussbaum gradually taught Wilson and Bailey-Wilson the administrative aspects of the chief's job; thus, they were well prepared to take over this year. "He trained us up," says Wilson.

Co-branch chiefs are rare at the NIH; married co-chiefs are even rarer. To their knowledge, Wilson and Bailey-Wilson are the only ones.

—Karen Ross

Symposium to Honor James Ferretti

A symposium honoring James Ferretti—"Forty Years of NMR in Biological Systems" will take place **April 21, 2006**, 8:30 a.m.–5:00 p.m., Natcher Conference Center, Balcony B & C.

Ferretti, a PI in the Laboratory of Biophysical Chemistry, NHLBI, pioneered the application of pulsed Fourier transform nuclear magnetic resonance techniques to the study of a wide range of chemical and biological systems of medical importance. His research reflects a multi-disciplinary approach to understanding molecular events in embryonic development.

Featured speakers include Ad Bax, NIDDK; Marshall Nirenberg, NHLBI; Dennis Torchia, NIDCR; and other internationally famed investigators from the United States and abroad.

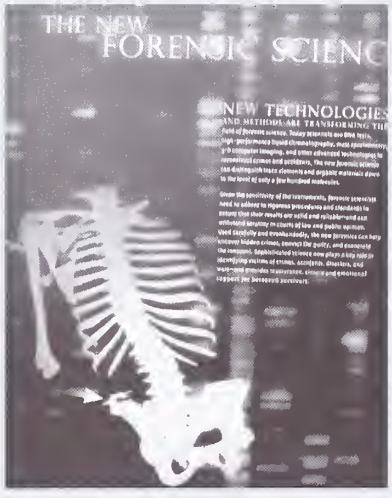
For more information, visit:

<http://www.nhlbi.nih.gov/meetings/ferretti>.

There is no cost to attend, but registration is requested. To register, contact Nico Tjandra, Building 50, Room 3503, (fax) 301-402-3404, e-mail: **<tjandran@nhlbi.nih.gov>**.

NLM's "Visible Proofs" Exhibit

"You are not to expect visible proofs in a work of darkness. You are to collect the truth from circumstances, and little collateral facts, which taken singly afford no proof, yet put together, so tally with, and confirm each other, that they are as strong and convincing evidence as facts that appear in the broad face of the day."
—Judge Francis Buller to the jury, Donnellan case, March 1781



On display at the NLM from February 16, 2006, to February 16, 2008, "Visible Proofs: Forensic Views of the Body" traces the development of forensics through historical hallways of artifacts, documents, and interactive and moving exhibits.

Enter the world of "Visible Proofs" at **<http://www.nlm.nih.gov/visibleproofs>**.

NCCAM Lecture: Acupuncture Ancient and Modern

The ninth in the NCCAM Distinguished Lectures series is set for **April 26, 2006**, from 11:00 a.m. to noon in Masur Auditorium, Building 10. Bruce Rosen, director, Martinos Center of Biomedical Imaging at Massachusetts General Hospital in Boston, and professor, Harvard Medical School, also in Boston, will speak on "Neurobiological Correlates of Acupuncture: Modern Science Explores Ancient Practice."

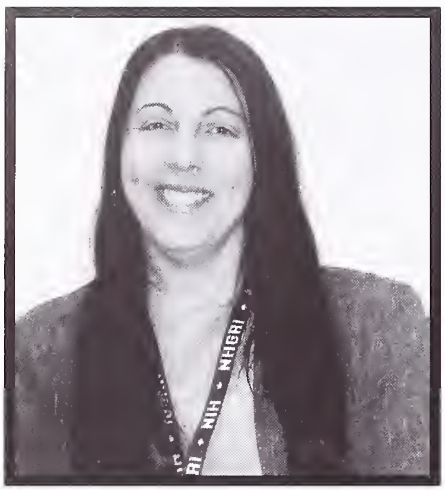
The lecture will be videocast at

<http://videocast.nih.gov/>

and sign language interpretation will be provided. For more information or for reasonable accommodations, call 301-594-5595 or the Federal Relay at 1-800-877-8339.

More information about the series can be found at

<http://nccam.nih.gov/news/lectures>.



Karen Ross

Joan Bailey-Wilson

"One of the big lessons for me from [my involvement in] the World Trade Center identifications was that in times of stress, it is very difficult for police officers not trained in family history data gathering to elicit accurate information from family members. Genetic counseling professionals are the people who can elicit accurate information about biological vs. social relationships within familes. Clinical geneticists, who often deal with severe diagnoses, are familiar with crisis counseling and appropriate interviewing techniques."

Fran Pollner

Lisa Forman

"When Katrina occurred, it was natural for the state crime lab people in Louisiana and Mississippi, who were charged with the responsibility of identifying the dead, to contact the people who had done that at the World Trade Center. . . .
That World Trade Center group—I have never seen such synergy, not in any other group I was ever involved in. Each person brought his or her perspective to the table; issues were always evolving [over the four years the group worked together]; it was an amazingly creative process. . . .
And now, once again, from the first meeting in November, this current group has the same energy and synergy."

DNA Identification of Hurricane Victims

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cane Victim DNA Identification Expert Group (HVDIEG) are NHGRI's Bailey-Wilson, co-chief of the Inherited Disease Research Branch; Les Biesecker, senior investigator, Genetic Disease Research Branch, and Elizabeth Pugh, director of bioinformatics and statistical genetics at the Center for Inherited Disease Research in Baltimore.

In the NLM/NCBI contingent are staff scientists Steve Sherry and Lisa Forman. Aside from his victim identification work, Sherry runs the NCBI single nucleotide polymorphisms database (dbSNP). Forman spends about half her time on DNA forensics and the other half on the genetics of rare disease.

It was Forman who, in her capacity as a forensics expert at the National Institute of Justice (NIJ), had assisted the New York medical examiner's office in organizing the KADAP in 2001; see "World Trade Center Victim Identification Pushes Frontiers of Forensic Science," *The NIH Catalyst*, September-October 2002, page 1.)

Forman developed close personal and professional ties with her KADAP colleagues over their four-year collaboration, and after the HVDIEG got underway—coordinated by Amanda Sozer, a forensics expert who had served on the KADAP and was working on high-throughput forensics for the state of Louisiana—Forman was recruited to NCBI, where she officially started in early February.

The Birth of OSIRIS

It was in July of 2003 that an NCBI-NIJ interagency agreement enabled Sherry to initiate his quest to develop the DNA quality-assurance tool that would become OSIRIS. And it was Forman's teenage son who suggested that this new entity be named Osiris, after the Egyptian god of the dead. The words encompassed by the letters in the name—open source independent review & interpretation system—fell easily into place.

The goal, Sherry says, was to address the inadequacies of existing machinery and software designed for use in a "pristine laboratory environment with robust samples and no contaminants"—hardly the situation on the ground at the WTC.

"A lesson learned from 9/11," Sherry says, "is that DNA profile data from samples in challenging environments yield suboptimal results."

"In any mass fatality," Forman observes, "there can be misalignment of identifications. There were false identifications at the World Trade Center early on; they were ultimately rectified, but it was very distressing for all concerned." The OSIRIS software, she says, provides programmatic checks and double-checks and "recognizes the intersections where errors can lead to misidentification."

Forensic assessment of identity and whole-SNP genotyping to decipher patient illness, Sherry notes, have similar accuracy requirements. "The software we're writing for OSIRIS will dovetail victim identification and genetic variation in illness."

A mass fatality can introduce noisy signals that are not part of a DNA profile. Conversely, if part of a sample is destroyed, the intensity of a true signal can be reduced to a point below the normal background cutoff. "We've created software that can semiautonomously adapt to the local characteristics of any dataset, provide its own data analysis, and differentiate noise from a real signal," Sherry says.

"We can digest thousands of samples and quickly identify the small handful —10 percent—of gray-area cases that must be set aside for human eyes to review."

Sherry has been assisting the coordinators of the HVDIEG program—Sozer and Tammy Pruet Northrup, the manager of the DNA unit of the Louisiana State crime lab—in readying OSIRIS to provide informatics support.

"We're building up a statistical profile and framework for victim identification that I'm comfortable with," Sherry says.

In the "developmental mode," OSIRIS is posted at a free and open website (see <**http://www.ncbi.nlm.nih.gov/IEB/Research/GVWG/OSIRIS/**>). In maintaining and updating the site, "Lisa will write the documentation; I'll do the artwork," Sherry says.

Victim Identification Obstacles In New York and the Gulf Coast

Before Sherry's first trip to Baton Rouge, NHGRI's Bailey-Wilson and Pugh had been at work on the scene helping state officials develop protocols for family history data collection and installing the relevant software for that project.

Their early presence there was a consequence of the havoc wreaked by Hurricane Katrina, which had created a very

different set of forensic circumstances from those surrounding WTC victim identification.

In New York, victim remains were often severely compromised, with full DNA profiles unavailable and body parts, rather than intact bodies, discovered in the wreckage. Reliable reference material, however, was abundant—victims' cups, hair samples, toothbrushes, and the like provided by local family members with relatively easily verified pedigrees and accessible DNA samples for comparison to the remains.

Many of Katrina's victims were recovered with intact tissues and articulated skeletons—but without the adjunct reference samples to establish their identity. Katrina had washed away homes and personal effects, disconnected the victims from those identifiable belongings that could have provided the needed match, making family reference material that much more crucial. But many families were broken up, dispersed throughout the region and even the country.

Thousands were reported missing and feared dead in the hurricane's aftermath because people had no idea where their relatives were or how to get in touch with them.

A Stream of Genetics Counselors

It became clear to Sozer and Northrup early on, Bailey-Wilson says, that many victims would require DNA identification and that genetics professionals would be the best people to contact family members, construct family trees, and explain the rationales and logistics of DNA sampling to those biological relatives whose samples would be most helpful.

Bailey-Wilson adds that for its part, NHGRI was pleased to support the activity and also recognized the opportunity the project offered for training clinical geneticists and counselors on staff and, especially, the genetics counseling students in the joint Johns Hopkins University–NHGRI training program.

With NHGRI's Barb Biesecker, director of the training program, Bailey-Wilson has organized volunteer expeditions typically for one-week stays at the Baton Rouge headquarters. NHGRI funded the travel and other expenses of the first sets of volunteer teams, after which NIH funds kicked in to continue the flow. At first only NIH was supplying genetics counselors; in February, the travel of non-NIH volunteers began to be supported by FEMA.

Bailey-Wilson trains all the volunteers, regardless of where they come from, typically by conference call. She orients them to the purpose of their work in Baton Rouge, which is to interview family members of missing persons and to ask the questions about family relationships that will distinguish biological from nonbiological members. She explains how forensic specialists use the genotypes of relatives to infer the genotype of the missing person, "like fitting pieces into a jigsaw puzzle."

The session takes no more than two hours because the volunteers have genetics counseling backgrounds. The time it takes for the volunteers to track down family members and to interview them, however, "varies immensely," she says.

With extended families or those widely scattered by the storm who have moved multiple times and may be staying in hotels or trailers, there's a lot of detective work involved.

Once the family structure has been determined and the DNA samples agreed to, the geneticists' work is done, and the state arranges for the samples to be taken wherever the individuals are.

DNA samples are genotyped for a set of highly polymorphic genetic loci traditionally used in forensic analysis; it's the job of the statisticians on the HVDIEG, Bailey-Wilson notes, to establish stringent criteria for evaluating match probabiliities.

She's learned a lot, she says, from her experiences on KADAP and HVDIEG—about cutting-edge genotyping methodologies, how to deal with degraded samples, and special statistical methods for dealing with unique problems that can arise in trying to impute the genotype of a missing or deceased person from a pedigree. "This work," she notes, "has a direct impact on my own cancer genetics research" (see "Marriage of the Minds," page 1).

There's also the less academic and more joyous rewards of helping families reunite and of being the bearer of good news to distressed people.

Most of the thousands of people reported missing by family members who called in to the Baton Rouge Find Family Call Center have been found alive. "Just about every geneticist who has

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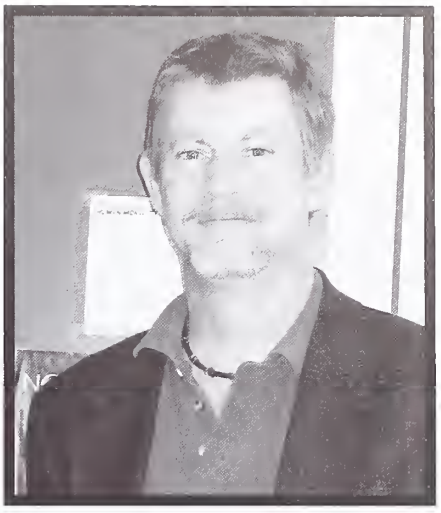


Fran Pollner

Steve Sherry

"I try to anonymize the data before regarding them scientifically. I work with the digital representation of victims through their DNA profiles. In that way, the objectivity of the science is not compromised—I am not confronted with the real names that call up the images of the real people, which for me is unbearable. . . . I am a product of the U.S. investment in science. I went to public universities and was trained in the theory of population genetics. What I am doing now—using the lessons of 9/11 to work on OSIRIS to ease the pain and suffering of families—is as close as I can imagine myself to being a clinical scientist. I cannot practice at the bedside, but I can do this, and this is my return on the public investment in my training—and my reward."

Celia Hooper

Les Biesecker

"At the end of the day, this effort is about helping families to come to grips with the loss of their loved ones and facilitate the grief process. Grief is one of the most fundamental of human emotions and it can be complicated when the loss of a loved one has any degree of uncertainty associated with it (i.e., were they really killed?) or the absence of the physical remains of that loved one. It is our job to untangle the grief process by providing families with unambiguous evidence of the loss to set them on the road to come to grips with the tragedy and their loss."

worked there, in the process of tracking down family members, has found one or two people reported missing who are alive. Every time someone is found alive, the finder rings a special bell, and everyone in the Center applauds. That little bell rang very frequently in December," Bailey-Wilson recalls.

"But the families being interviewed now," she adds, "are those whose missing person still has not been found, and most will need a DNA identification and most, it's my impression, are desperate."

Tomorrow

One day in February, Sherry accompanied two FEMA officers on their rounds in the devastated Lower 9th Ward of New Orleans. Their task was to search the premises at addresses of people reported missing who had yet to be found. They were looking for remains.

They came upon three kinds of scenes: empty space where once there had been an address, standing homes that had been cleaned up by family members, and standing homes filled to the brim with rubble so dense as to make passage difficult—the kind of scenario that could harbor a missing person.

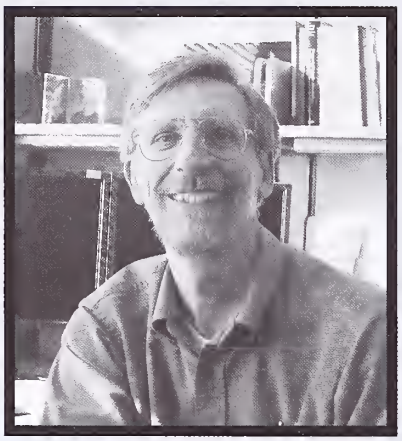
In fact, in such a home only the day before had been found the intact pajama-clad remains of a man in a bed buried under heaps of debris.

So long as such findings are possible, the issue of razing all the uninhabitable residences is problematic, Sherry remarks. Bulldozing, he says, could crush, disarticulate, and blend hidden remains, complicating the ensuing identification efforts.

It has been projected that HVDIEG objectives will have been reached within the year, and Sherry will continue providing his services as long as they are needed. With regard to OSIRIS and assuring the quality of genotype data, he says, "there is no severance date—that's an open-ended commitment."

A similar commitment has been made by the New York medical examiner's office regarding the disposition of remains tagged but not yet identified—a little less than half of the WTC victims. The remains are dessicated and vacuum sealed for maximum preservation, to be entombed collectively in a memorial structure—and, says Sherry, ever available for identification should new technology emerge that can extract meaningful DNA fragments from material now unreadable. ■

Reading the Small Print To Answer Some Big Questions



Fran Pollner

Jim Ostell

There are many reasons for NCBI's commitment to aid in the identification of the Gulf Coast hurricane victims, not the least of which is that the work contributes to the center's scientific mission, says Jim Ostell, chief of the NCBI Information and Engineering Branch and the person who okays the Gulf Coast activities of the involved NCBI scientists.

Aside from those motives based in the immediate humanitarian imperative, there are the extraordinary scientific rewards of pursuing the research that builds the sequence-analysis tools used by basic scientists. Beyond that, these tools are moving data from the computer screen into the realm of human health.

"It's not just academic any more," observes Ostell. "We're moving into a stage at which the molecular biology of the sequences of the human genome—and of bacteria and viruses—are becoming tools in medicine."

One of the first applications of bioinformatics was in refining the tissue typing data upon which bone marrow registries rely for matching donor and recipient. As sequence databases expand and more allele subtypes emerge, standing registry data become less than optimal.

Original data from the sequences used in any tissue typing test kit can be run through the NCBI database and signals of otherwise hidden little bits of DNA can be amplified—or not—for more precise characterization.

"Without going back to the human involved, taking more bone marrow, or endangering the recipient, we can instantly increase the likelihood that a transplant will succeed," Ostell notes.

In collaboration with NIAID, NCBI is sequencing the genomes of flu viruses isolated from patients and tracing their molecular evolution. "We can see how viruses are related to one another, derived from one another." Through understanding the natural history of viruses of interest and maintaining surveillance, scientists can predict the rate at which a virus will likely evolve into an entity against which a vaccine would be warranted.

Viral surveillance, he notes, has implications not only in the traditional public health domain but also in the bioterror field that has become part of the landscape.

And specifically related to problem solving in the identification of victims of mass disasters has been the development by NCBI's Steve Sherry of OSIRIS (open source independent review & interpretation system).

Conceived in the ashes of the World Trade Center and under development for the past three years, OSIRIS is being tested on the ground in the Gulf Coast and is still evolving, according to Sherry (see "Forensics Meets Medical Genetics . . .," page 1).

OSIRIS, says Ostell, is a prime example of an advanced informatics research tool to analyze signal variations that will exert wide impact, ensuring that sequencing and mapping machines yield high-quality data, with particular use in forensics and medical genotyping.

NCBI, Ostell observes, has grown in tandem with the bioinformatics field. Established as a part of NLM in 1988, with 12 people, no website, and CD-ROM as the means to release the first databases generated, it now boasts "two million unique users daily, with peak rates of 2,000 web hits a second." It is at the epicenter of translating the data amassed from the Human Genome Project and has served as a first responder to the DNA identification demands arising from manmade and natural disasters.

"In the event of future mass fatalities," Ostell notes, "there will be some new wrinkles, yes, but the response will be more routine because the protocol has been established." He hastens to add, however, that "there's quite a bit left to do—there's always something else."

—Fran Pollner

NHLBI Lab Provides Port in Katrina Storm

by Tara Kirby

Late last summer, when Hurricane Katrina devastated New Orleans and the Gulf Coast, research at Tulane University in New Orleans and other institutions was imperiled too. Not only were researchers displaced from their laboratories, but also in many cases equipment and irreplaceable research materials were lost.

NIH quickly responded to the humanitarian and medical needs of those affected by Katrina. (See editorial, "Responding to Hurricane Katrina," *The NIH Catalyst*, September-October 2005, page 2.)

It was also recognized that researchers would need help to continue (or even salvage) their research programs. In addition to special policies for affected NIH grantees, NIH extended help from its intramural program.

In a memo dated Sept. 4, 2005, Deputy Director for Intramural Research Michael Gottesman encouraged investigators to "provide research homes" for displaced researchers and their trainees. Scientific directors were asked to help intramural investigators with logistics and financial support for bringing Gulf Coast colleagues to NIH.

Mark Knepper was one investigator who responded to this call. Chief of the Laboratory of Kidney and Electrolyte Metabolism at NHLBI, Knepper encountered a colleague at an American Heart Association meeting in late September—L. Gabriel Navar, chair of the Department of Physiology at the Tulane University School of Medicine. Navar had relocated to the University of Mississippi Medical School in Jackson, Miss., to regroup after the hurricane.

Navar introduced Knepper to his postdoctoral fellow, Fady Botros, who needed a space to work, as well as computer and library resources, to revise a paper and plan future experiments. Botros had returned to the New Orleans suburbs a week after Katrina hit and had been attempting to work at home. Knepper offered to host Botros, and while the offer was effortless, the administrative arrangements "turned out to be pretty tricky," Knepper recalled in an interview with *The NIH Catalyst*.

But, as the saying goes, where there's a will, there's a way. NHLBI was committed to helping displaced researchers, and Scientific Director Robert Balaban "said 'Do it'," reported Knepper. "We had Fady on a Washington-bound plane within three days."

Botros arrived at NIH on October 10 and spent three weeks in Knepper's lab. He exchanged ideas with people in the lab and learned about the NIH intramural program. Botros also presented a talk on his research at Tulane—the role of heme oxygenase in regulating renal microcirculation and renal function. In addition to the mutually beneficial interactions with Knepper's group, Botros also received material support. "NHLBI was generous" in providing support for his visit and travel expenses, he says.

In early November, Botros returned to Louisiana. Knepper observed, " I would have been happy to have him stay much longer, but he needed to go back to rejoin his wife"— a Ph.D. student at Louisiana State University displaced to Baton Rouge—"and help in the cleanup." Botros took back the fruits of his collaboration—protocols and antibodies for his future studies. He looked forward to continuing his collaboration with Knepper, but "everything was delayed," he said, "because the situation was worse than I expected" when he returned to New Orleans.

Mark Knepper *Fady Botros*

It would be several months before Botros could continue his research. When he returned to New Orleans, recovery efforts by his labmates were stymied because the facilities and power plant were still nonoperational. It was not until early December that they were allowed to retrieve items from the lab spaces. "We could go in twice a day for an hour each time and under supervision," explained Botros, "because the building was not safe."

Navar's group members returned to their lab in January, but still could not conduct experiments due to continued utility outages. Botros was finally able to restart his research on February 7, more than five months after Hurricane Katrina hit New Orleans. Still, he was one of the lucky ones; two-thirds of the medical school was still closed at that time, he said. Some investigators were able to find temporary work space in those buildings that were open.

Navar noted the need still in early March for major electrical work to reroute the main control panels and generators, but he anticipated that the entire medical school would be open by the end of that month. He praised Knepper and NHLBI for their "gracious assistance" and expressed gratitude for the many groups and individuals who rushed to support the Tulane research community.

Botros calls his time at NIH "a great research and life experience." He was "happy," he says, "to be in a normal research environment after the disruption" visited upon him and his labmates.

Knepper downplays his own role and credits "the nature of the NIH community to be open, compassionate, and eager to share. Many, many people," he said, "helped to make Fady's visit possible." ■

NIH Community Response

Records are spotty, but at least 20 other NIHers offered lab and/or housing space to researchers displaced by the hurricane or the families of patients dispatched to the Clinical Center. Hundreds volunteered to provide needed services on-site in the Gulf Coast. And the postbac community organized relief efforts that resulted in the shipment of money, household supplies, toys, clothing, and food to the Gulf Coast, as well as more than 30 large boxes of clothing and food to a local charity working with people evacuated to the Washington, D.C.-Maryland area. ■

Accomplishments and Goals of the NIH Assembly of Scientists (AOS)

This is the first in what will be a continuing AOS column in The NIH Catalyst *to address issues of concern to NIH scientists. The views expressed are those of the signer. Individuals who wish to write a column should contact a member of the ViewPoint editorial board (Abner Notkins, chair; Harvey Alter; Edward Korn; Alan Schechter; Joshua Zimmerberg). More information about the AOS can be found at its website:* **<http://aos.fastflag.com/>**.

It was a dark and stormy fall night, and I was sitting in an airport lounge at Dulles—frustrated. Frustrated at the hours-long rain delay of my flight, but more frustrated at what was happening all around me at NIH. So I plugged in the computer and tried to put words to feelings that I was pretty sure were shared by others.

What emerged was a draft letter, whose intended recipient was NIH Director Elias Zerhouni, that focused on the severe restrictions on the ability of NIH scientists to speak and interact with the extramural community that were instituted in the wake of the Congressional hearings about NIH scientists who had financial interests with drug companies. I circulated the letter to a haphazardly selected group of NIH scientists. Thankfully, they substantially edited it before it was circulated more widely around NIH. It collected nearly 200 signatures in just a few days.

Reacting to this letter, Dr. Zerhouni scheduled a meeting at the end of November 2004 at which NCI's Lee Helman presented the scientists' view, a position echoed spontaneously by many others in attendance.

The AOS Gets Going

And the rest, as they say, is history. In February 2005, the NIH Assembly of Scientists was reconstituted, and elections were held for an Executive Committee. (A complete history of the AOS will appear soon in a subsequent column.) Simultaneously, DHHS issued the "interim final" conflict-of -interest rules. Meeting virtually every week from February to July, the AOS Executive Committee—composed of scientists who understand NIH's culture by dint of many years and decades of service—began an intense effort to educate the public, professional societies, the media, and others about the serious adverse consequences of these new regulations and to devise alternative rules. It also drafted new bylaws and planned the elections of the "real" Assembly of Scientists' Council.

What has been accomplished? The first and most important accomplishment was changing the atmosphere around the conflict-of-interest issue. When the rules were initially issued, few inside or outside the NIH read and analyzed them to understand how unjustifiable they were. To oppose them seemed to some to be equivalent to opposing ethics, motherhood, and apple pie. Fortunately, the AOS executive committee was able to craft a message that made it clear that we found it reprehensible that some NIH scientists had conflicts of interest and that we endorsed absolute prohibitions on such—but also that we opposed unjustified restrictions that undermined the NIH's ability to recruit and retain scientists. Changing the atmosphere was an absolutely essential prerequisite to changing the rules.

Ezekiel Emanuel

The second accomplishment was that the Executive Committee proactively devised and proposed a reasonable conflict-of-interest policy as a substitute for the Draconian "interim final" regulations. This alternative aimed to prohibit conflicts of interest without over-reaching. The preamble to the final rules issued in August by DHHS makes clear that the AOS' recommended policy informed the revision. Obviously, the rule changes were not accomplished by AOS alone but required substantial efforts by the NIH administration to craft the reasonable changes.

The third accomplishment was structural: reconstituting the AOS, drafting new bylaws, holding an election in October 2005 for the new AOS Council, and, most recently, electing an Executive Committee. Nearly 700 NIH scientists voted, giving NIH intramural scientists a legitimate collective voice that had been lacking.

Finally, one of the most important accomplishments was more procedural. Much of what has been accomplished was the result of the collective wisdom of the original 17 members of the AOS Executive Committee. Discussions usually encompassed a wide variety of views and were, on occasion, even heated. No person was right on all the issues, and all of us learned from the perspectives of people we disagreed with. We were repeatedly able to generate a consensus around what we considered to be the wisest and most prudent decisions, avoiding what could have been disastrous missteps. This was a triumph of open and deliberate governance in which the group proved consistently wiser than any single person.

What Lies Ahead

Frequently, after the change in the conflict-of-interest regulations, reporters would ask whether with this "victory" the AOS could declare "mission accomplished" and go home. This reflects a serious misunderstanding. The conflict-of-interest regulations were only the nidus that crystallized the frustrations of NIH scientists. There are many serious issues that still need addressing. Regarding the conflict-of-interest issue:

- *There is implementation.* Scientists have been promised less paperwork and an electronic system for submitting activities. What we have experienced is the opposite, symbolized by the 716 form. Furthermore, the implementation committee—which was established to help implement the new conflict rules and has two members that serve on the AOS Council—does not appear to have real authority to address the problems and thus far has made little progress.
- *There is the matter of consulting.* For the last 16 months, there has been a moratorium on consulting to permit a systematic review of its merits and risks. The AOS believes this review is critical and should proceed as rapidly as possible.
- *There is the conflict-of-interest impact assessment.* Through a survey of NIH scientists and a systematic assessment of departures and challenges to recruiting, the NIH is to assess the impact of these regulations. The AOS thinks that once the survey is completed, it is important for NIH scientists to participate in the assessment of the data and the development of solutions to the problems.

Importantly, there are many other issues beyond conflict of interest that are sapping morale and the ability to attract and keep first-rate scientists. Travel policies, the continued employment at NIH of scientists and nurses retiring from the PHS, the ever-growing nettlesome bureaucracy, and the lack of decision-making transparency are all of great concern to the AOS.

It is our hope that the AOS—which lies outside the formal NIH chain of command and can work with the deputy director for intramural research, the scientific directors, and outside professional organizations—will provide a clear voice to help reduce the bureaucratic frustrations of working at NIH and to ensure that top-quality science continues to be done on campus in a collegial and collaborative atmosphere that ensures scientific and personal integrity without restricting scientific and personal freedom.

—Ezekiel Emanuel, Director
Department of Clinical Bioethics, CC

NIH History: Giulio Cantoni and Music at the NIH

"Music is the effort we make to explain to ourselves how our brains work."
—*Lewis Thomas*

by Henry Metzger

Giulio Cantoni (1915–2005) was chief of the Laboratory of General and Comparative Biochemistry, NIMH, from 1954 to 1994. He retired as scientist emeritus in 1996—but he continued until his death as the director of the FAES (Foundation for Advanced Education in the Sciences) chamber music concert series he founded at NIH in 1968.

A Jewish Italian physician who fled Italy with his family in 1939, Cantoni was interned in England and Canada before gaining entry into the United States in late 1941, aided by conductor Arturo Toscanini, a family friend.

Among Cantoni's scientific achievements were his pioneering studies elucidating the process of methylation, including the discovery of the active co-factor S-adenosylmethionine.

A memorial symposium honoring Cantoni's diverse accomplishments took place on the NIH campus February 9, 2006. It was sponsored by NIMH and FAES. Scientist Emeritus Henry Metzger, FAES president and former NIAMS scientific director, delivered a historical recap of the origins of FAES on the NIH campus and its eventual emergence, by dint of Cantoni's managerial baton, as a highly acclaimed venue for music. Following is an adapted version of Metzger's tribute to Cantoni.

Giulio Cantoni

The FAES was formally created in 1959 for the purpose of promoting, as its name indicates, advanced education in the sciences. In preparation for my remarks today, I did a bit of historical research on how Giulio and the FAES developed their collaboration. I reviewed the minutes of the meetings of the FAES Executive Committee and Board of Directors as well as Giulio's own account.

For the first five years, all of the discussions at the meetings of the governing bodies of FAES were about the courses to be offered, the possibility of having a formal degree-granting program, creating a bookstore for scientific texts, and especially creating a faculty center. It was in the context of developing detailed plans for such a center that the first reference to cultural activities appears, in 1964. As chair of a Committee on Cultural Activities, Seymour Kety (who in 1951 had become scientific director of both NIMH and the National Institute of Neurological Diseases and Blindness) suggested the cultural activity of including a bar for that center.

1964 also marked what appears to have been the first NIH Cultural Lecture—the FAES-sponsored appearance of Washington humorist Art Buchwald. (While on sabbatical in Paris some years later, I had a chance to test Buchwald's presentation of how to see the Louvre in less than three minutes.)

The next reference to cultural events comes after Leonard Laster took over as chair of the committee and reported that: "Emma Kountz presented a concert of 'Beethoven's Legacy to Man' on December 15, 1966 [shortly before the 140th anniversary of Beethoven's death] . . . . Dr. Cantoni arranged for Mrs. Kountz to appear at NIH and he was enthusiastic about offering additional concerts."

A year and a half later, in the spring of 1968, at the invitation of Giulio, the world-famous ensemble Virtuosi di Roma presented an all-Vivaldi program at NIH. This was the first of the series initiated by Giulio of what to date includes more than 300 chamber music concerts. The concerts have included instrumentalists and vocalists from almost every European country as well as from Japan. For three, the NIH concerts were their U.S. debut. The Washington debut of another 26 featured such world-renowned artists as Maurizio Pollini (1971), Radu Lapu (1974), Viktoria Mullova (1987), and Ignat Solzhenitsyn (1992).

It was in the 25th year of the series that Giulio penned a chronicle of the origins and unfolding of this cultural enclave in the halls of advanced scientific education. He called this summary and listing of participating musicians "Il Catalogo," after Leporello's first-act aria in Don Giovanni. Giulio translated the opening line as "This is the catalogue of friends we loved." (For those in the know of who was on that list of Don Giovanni's international friends, and how he befriended them, the nature of Giulio's sense of humor is clear. For those unfamiliar with the opera, the aria relates the number of international seductions credited to the Don.)

In his synopsis, Giulio recounts how music had been an essential part of his life ever since his adolescent days in Milan, when he was exposed to good music through the public performances of a local amateur society.

He recounts also that when he and his wife, Gabriella, moved to Bethesda in 1954 there was a paucity of musical events in the Washington area and that when in the early 1960s he tried organizing some musical lectures, their reception was less than enthusiastic. However, when he and his wife assisted in fundraising for the Save Venice Committee after the disastrous flooding of Venice and Florence in 1966, public response was heartening. He states:

"The successful results of these efforts were very rewarding. . . .The realization that the public might respond to appeals in support of cultural initiatives brought about a gradual change in my attitude. By the early spring of 1968, with the invaluable encouragement and support of my wife, I became convinced that the organization of a series of chamber music concerts at NIH might be feasible, provided FAES would supply the necessary sponsorship."

He notes that a critical element in his decision was the arrival of Paola Saffiotti, whose husband Umberto had been recruited to NCI. She had worked in Italy as a representative of some world-renowned artists. Giulio details her "invaluable collaboration" in generating the series.

Giulio and Paola shared the objective of presenting both well-known artists at the peak of their careers and promising junior performers. Those of us privileged to have attended these concerts over many years can attest to their continued success in achieving their goal. I might mention that Paola has finalized the program for the 39th season in 2006-2007, in the formulation of which Giulio still played a major role [see "Services" at <**http://www.FAES.org**>].

Over the years, as NIH grew and many of us became more specialized and seemed to find less time to interact with colleagues outside our own areas of interest, the concert series not only gave us a superb cultural experience but also a venue for pleasant collegial interaction. In addition, the compatible mix of attendees who were NIH retirees as well as simply individuals from the surrounding neighborhood created an aura of good feeling and community.

And there was also the fellowship that developed among the musical artists and the scientists: "We are proud and happy to regard them as friends," Giulio wrote in "Il Catalogo." ■

Recently Tenured

Kim Hasenkrug *received his Ph.D. in cell biology from the Albert Einstein College of Medicine in New York in 1991. He did postdoctoral training in the Laboratory of Persistent Viral Diseases, NIAID, and became a tenure-track investigator in 1998. He is currently a senior investigator in the Laboratory of Persistent Viral Diseases at Rocky Mountain Labs.*

Despite the remarkable capacity of the immune system to recognize and clear most infectious agents, we are all chronically infected with viruses that have escaped immunological eradication.

Kim Hasenkrug

Although most chronic viral infections are relatively innocuous, immunological escape of viruses such as hepatitis C virus and the human immunodeficiency virus causes a great deal of morbidity and mortality worldwide.

During my postdoctoral studies in Bruce Chesebro's laboratory, I investigated genetic resistance to Friend virus infection in mice and found that even the most resistant strains of mice were unable to completely clear infection.

I became fascinated with the problem of chronic infections and realized that a better understanding of the basic mechanisms by which this retrovirus established and maintained persistence could aid in the development of vaccines and therapies against some of our most dangerous viruses.

Much of my early work focused on using the Friend model to determine mechanisms of protection by live-attenuated vaccines. It was known that live-attenuated simian immunodeficiency virus (SIV) provided the best vaccine protection from SIV in the nonhuman primate model for HIV, but that model was not well suited for mechanistic studies.

Using live attenuated Friend virus we showed that complete protection, defined as protection from both acute disease and the establishment of chronic infection, required immune CD4+ T cells, CD8+ T cells, and also virus-neutralizing antibodies.

Each of these components provided essential, nonoverlapping functions. Although live-attenuated vaccines are considered too dangerous to use as vaccines in humans, the description of how live-attenuated Friend virus worked provides an experimental framework indicating the types of responses required for a successful retroviral vaccine.

In addition to prevention of chronic infections, I have also been very interested in immune control of established chronic infections.

We found CD4+ T cells and IFN-γ to be crucial for control of chronic Friend virus and the prevention of relapses. Interestingly, although CD8+ T cells were critical for recovery from acute infection, they played no role during chronic infection.

As we began to probe more deeply the functions of CD4+ and CD8+ T cells during chronic infection, we made the intriguing discovery that chronic infection induced regulatory CD4+ T cells that suppressed CD8+ T cell functions.

Subsequently, other labs reported similar findings for HIV and other chronic viral infections in humans, suggesting that the induction of regulatory T cells may be a common mechanism of escape.

Now that we have determined why the CD8+ T cells are impotent, our studies are focused on determining the molecular mechanisms of suppression, both at the level of the CD4+ regulatory T cells and the CD8+ effector cells.

We recently developed an in vitro suppression assay to facilitate our mechanistic studies, and results recapitulate much of what we observe in vivo.

We are also using our in vivo model to determine ways to specifically inhibit the regulatory T cells, render the CD8+ T cells resistant to suppression, and reactivate immune responses during chronic infection. Our goal is to modulate the immune response to enable the complete clearance of chronic infections.

We recently achieved thousand-fold reductions in chronic Friend virus levels using immunocytotherapy combined with CD137 co-stimulation.

We will use the data from our mechanistic studies to further develop and refine our immunotherapeutic approaches, and we hope to translate our findings to therapies for chronic infections in humans.

Lenore Launer *received her Ph.D. in epidemiology and nutrition from Cornell University in Ithaca, N.Y., in 1987. After a postdoctoral fellowship at NICHD, she held academic appointments in the Netherlands at Erasmus University Medical School in Rotterdam, Free University in Amsterdam, and the National Institute for Public Health and the Environment, Bilthoven, before joining NIA in 1999 as chief of the Neuroepidemiology Section. She is currently a senior investigator and chief of that section in the Laboratory of Epidemiology, Demography, and Biometry, NIA.*

My main contributions to the study of the epidemiology of dementia have been to identify cardiovascular risk factors of late-life dementia and the value of studying these risk factors in midlife. Another research focus has been to elucidate the relationship of migraine to structural brain changes in midlife.

I started my research on the epidemiology of brain aging in 1990, when I accepted an appointment at Erasmus University in the Netherlands. There I worked as a research scientist on a community-based study of dementia. I was also the scientific coordinator of multicenter prospective studies on the epidemiology of dementia involving a consortium of major European centers.

Lenore Launer

While in the Netherlands, I established a population-based cohort of individuals with and without migraine for the study of migraine-related risk factors and structural brain changes.

My research program since joining NIA in 1999 has focused on the interaction between the vascular and neuronal systems as reflected in biomarkers of subclinical and clinical disease. Related cognitive function studies and structural measures of brain neuropathology in large population-based studies have been important in these investigations.

Thus far, my research has shown that vascular dementia and Alzheimer's disease—currently diagnosed as two different types of dementia—share common risk factors, such as smoking, hypertension, diabetes, and elevated C-reactive protein.

This clinical picture is further corroborated by findings from an autopsy database, which I maintain in collaboration

with investigators in the Honolulu Asia Aging Study (HAAS).

The clinical and pathologic characteristics of brains in older persons suggest that by old age, a human brain has accumulated different types of vascular and neurodegenerative lesions, all of which may contribute to the clinical picture of dementia.

Further, based on the HAAS, I have shown that risk factor profiles in midlife are associated with the risk for late-life brain aging, suggesting that neurodegenerative processes begin earlier than previously thought.

My research aims in the coming years include disentangling the heterogeneous pathology, on the one hand, and the shared risk factors, on the other, of subtypes of dementia.

Using bioimaging, molecular markers, and clinical measures, I intend to identify brain-aging traits that cluster within and across biologic systems.

I will also investigate the interaction between genetic and environmental markers of vascular health, inflammation, cellular nutrition, and oxidation as they relate to brain-aging traits, as well as explore the role of early-life experiences in shaping the trajectory of brain aging.

These questions will be tested not only in the HAAS, but also in two studies I have been involved in since coming to NIA. The first, which is jointly led with Tamara Harris, NIA, is AGES-RS (Age Gene-Environment Susceptibility–Reykjavik Study). This is a large population-based study established in 1967 by the Icelandic Heart Association and conducted in Reykjavik.

Beside the advantage of a relatively genetically homogeneous population and excellent collaborators, we have data on early-life experiences of the cohort, through both the Reykjavik Study exams in midlife and the archival material available in Iceland.

AGES-RS focuses on four systems that are vulnerable to aging and disease—the neurocognitive, cardiovascular, musculoskeletal, and metabolic/body composition systems. Base-line data collection on about 5,800 men and women has just been completed, and a follow-up is in planning. This study is also supported in part by other collaborators in the NIA, NEI, NIDCD, NHLBI, and NINDS programs.

The second study I'm involved in is ACCORD, the largest randomized treatment trial in older people with diabetes; it's funded by NHLBI to test the efficacy of intensive *vs* standard treatment in reducing cardiovascular disease and mortality in diabetics.

I have added a cognitive and an MRI component to investigate whether interventions that aim to maximize improvement in hyperglycemia, blood pressure, and lipid levels result in a change in brain function and structure.

Thus, through observational studies and randomized trials, I hope to better understand how vascular factors play a role in common late-life dementia and whether there are avenues to pursue for intervention.

Zheng-Gang Liu *received his Ph.D. from the University of Massachusetts, Amherst, in 1995 and carried out his postdoctoral training in the laboratory of Michael Karin at the University of San Diego. He joined the Department of Cell and Cancer Biology, NCI, in 1998 as a tenure-track investigator and is currently a senior principal investigator at the Cell and Cancer Biology Branch, CCR, NCI.*

My training has been in the field of apoptosis and signal transduction, focusing first on the regulation of activation-induced apoptosis of T cells and then on cellular stress-induced JNK activation and TNF signaling.

Fran Pollner

Zheng-Gang Liu

Since coming to NCI, my research has focused on two themes:

1) Molecular mechanisms of TNF signaling. TNF is a proinflammatory cytokine that plays a critical role in diverse cellular events. Under the influence of TNF signaling, cells may variously undergo proliferation, differentiation, and apoptosis.

In the past few years, my group has made several critical discoveries about TNF signaling. For instance, we found that the key effector molecule of TNF signaling, RIP, is cleaved by Casps-8 during apoptosis and that this cleavage plays a major role in modulating the outcome of life and death in TNF-treated cells.

Moreover, RIP cleavage is a key factor in switching the path of cell death from necrosis to apoptosis. In addition, we also found that TRAF2, another key effector of TNF signaling, recruits IKK complex to TNFR1 complex to activate the NF-κB pathway.

Currently, my group is studying mechanisms of TNF-induced necrosis. I am especially interested in what controls the switch between apoptosis and necrosis in cells after TNF treatment.

2) Regulation of apoptosis. Apoptosis, or programmed cell death, is a common phenomenon during development and occurs to rid the organism of harmful or unwanted cells. Apoptosis is crucial in enabling organisms to maintain cellular homeostasis. Deregulation of apoptosis is involved in many diseases; for instance, inefficient apoptosis has been found in many different cancers.

Since all cells have the genetic machinery required to commit suicide, the ability to selectively regulate this process has profound implications for treating disease.

Because more and more evidence indicates that irregular cell growth often leads to apoptosis, we believe that in addition to promoting growth signals, inactivation of apoptosis is essential for normal cells to become tumor cells. This process can be achieved by either increasing a signal that actively blocks apoptosis or generating a defective mutation in the cell death machinery.

Identification of these apoptosis-inactivating targets in different cancers will greatly enrich our knowledge of tumorigenesis and help inform the development of new cancer therapies.

To that end, a major research interest of mine is to identify the genes that protect cancer cells from apoptosis and decipher the mechanisms of their actions.

Tom Misteli *received his Ph.D. from the University of London, U.K., in 1995 and was a postdoctoral fellow at the Cold Spring Harbor Laboratory, N.Y. He was recruited to the Laboratory of Receptor Biology and Gene Expression, NCI, in 1999. He now leads the Cell Biology of Genomes Group.*

Much progress has been made during recent decades in deciphering genome sequences and elucidating the basic molecular mechanisms involved in gene regulation. Although these efforts have

Recently Tenured

been very successful, they have also made it clear that these pieces of information are insufficient to understand how genomes work in vivo.

To do so, we must understand genome function at a global scale, and we need to uncover how genomes function in the context of the cell nucleus in living cells.

My laboratory seeks to elucidate the fundamental principles of how genomes are organized in vivo and how this organization contributes to gene regulation.

Fran Pollner

Tom Misteli

To begin to analyze the cell biological properties of genomes, we developed in vivo imaging methods to study the dynamics of gene expression for the first time in living cells.

Using these tools, we discovered that almost all aspects of nuclear organization and function are highly dynamic. For example, we were able to show that transcription factors find their specific binding sites within the genome by simple 3-D diffusion during which they scan the genome for their preferred binding sites.

Our measurements of interaction dynamics of proteins revealed that most transcription factors interact very transiently and rapidly with chromatin inside of living cells. These findings have led to a paradigm shift in how we think about gene expression in that they indicate that most regulatory gene expression events are stochastic.

The methods we developed have now become standard tools in the field and are powerful approaches to interrogate how genomes function in vivo. Our current efforts are aimed at visualizing and measuring the dynamic interplay of a complete transcription complex in a living cell and understanding how polymerases are dynamically regulated in vivo.

To this end, we are combining in vivo imaging methods with computational stimulation and modeling techniques to gain a quantitative view of gene expression in a living cell.

A second aspect of our work addresses the fundamental question of how genomes are spatially organized inside the cell nucleus. This is of great relevance because it is now clear that the position of chromosomes and of single genes within the nuclear space is nonrandom.

Our studies have contributed to the idea that how genomes are organized in the nucleus is related to their functional status.We showed that chromosomes are arranged differently in different tissues and that their position within the nucleus changes during differentiation.

One of our most import findings was the discovery that the position of chromosomes near each other contributes to the formation of cancer translocations in which chromosomes break and undergo illegitimate joining events, giving rise to fused chromosomes.

We are now expanding these studies by developing experimental systems in which we can induce and follow in single cells the fate of damaged chromosomes. These systems will allow us to query the cell biological mechanisms that lead to formation of cancer translocations.

These studies have clearly demonstrated that the cellular organization of genomes is critically important for proper genome function. One of the most important questions now is to understand how the fundamental principles of nuclear organization contribute to physiological genome function.

David Waugh

To address this problem, we are investigating how genome organization is established, maintained, and altered in physiological processes, including various diseases and during differentiation. These efforts will ultimately lead to an understanding of how genomes actually work inside of living cells.

David Waugh *received his Ph.D. in biochemistry from Indiana University, Bloomington, in 1989 and was a postdoctoral fellow at the Massachusetts Institute of Technology before becoming director of the Macromolecular Engineering Laboratory at Hoffmann-La Roche in 1991. In 1996, he established the Protein Engineering Section at the NCI-FCRDC. He is currently head of that section and a senior investigator in the Macromolecular Crystallography Laboratory, NCI-FCRDC.*

My research is divided roughly equally between two main projects: 1) "maximum likelihood" methods for protein expression and purification and 2) structural proteomics of type III secretion (the transport of virulence factors from the pathogen directly into the host cell) in *Yersinia pestis*, the causative agent of plague.

It is widely recognized that poor solubility of recombinant proteins in heterologous expression systems is a major bottleneck in structural and functional proteomics projects.

Although I was not the first to recognize that the solubility of recombinant proteins can sometimes be improved by fusing them to highly soluble partners, my section conducted the first systematic study of this phenomenon under rigorously controlled experimental conditions.

This work led to the discovery that *Escherichia coli* maltose binding protein (MBP) has an amazing ability to improve the solubility and promote the proper folding of its fusion partners.

These early experiments also shattered the dogma that any highly soluble protein can function as a solubility enhancer; the two other soluble fusion partners that were tested in this study, glutathione S-transferase (GST) and thioredoxin, were far less effective than MBP.

The current objective of my research in this area is to learn why some highly soluble proteins are much more effective solubility enhancers than others. I believe that understanding the underlying mechanism of the solubilizing effect is the key to realizing its full potential as a means of circumventing the inclusion body problem.

Although MBP is a powerful solubility enhancer, it is not a particularly good affinity tag for protein purification. For this reason, my group experimented with the incorporation of supplemental affinity tags within the framework of an MBP fusion protein.

The main challenge, from an engineering standpoint, was to identify locations in which accessory tags could be placed without interfering with the ability of MBP to enhance the solubility of its fusion partners.

Fortunately, it was possible to identify several permissive sites for the ad-

dition of accessory tags. This enabled us to explore various strategies for generic protein purification, and our efforts have recently culminated in the development of a simple process using a dual His_6-MBP tag that appears to be suitable for automation.

The MBP moiety improves the yield and enhances the solubility of the passenger protein while the His-tag facilitates its purification.

Recognizing that most affinity tags have the potential to interfere with structural and functional studies, we also assumed a leading role in the development of tobacco etch virus (TEV) protease as a reagent for removing affinity tags.

We have shown that, contrary to popular belief, many different amino acid side chains can be accommodated in the P1′ site of a TEV protease recognition site with little or no impact on the efficiency of processing.

The wild-type protease readily cleaves itself at a specific site to yield a truncated enzyme with greatly diminished activity, but we managed to overcome this problem by making amino acid substitutions in the vicinity of the internal cleavage site.

We also determined the crystal structures of TEV protease complexed with a peptide substrate and an inhibitor, which revealed the structural basis of its stringent sequence specificity.

Our success in producing large quantities of crystallization-grade proteins led to a small-scale structural genomics project aiming to solve the three-dimensional structures of proteins involved in type III secretion in *Y. pestis*.

Because the type III secretion system (TTSS) is essential for virulence, the resulting structural information could be used to develop effective countermeasures for this potential instrument of bioterrorism.

We have already solved 12 novel structures and are in the process of solving more, including several protein-protein complexes. In one case, we have already begun the process of structure-based drug development.

One of the cytotoxic effector proteins that *Yersinia* injects into mammalian cells via the TTSS—YopH—is a potent eukaryotic-like protein tyrosine phosphatase (PTPase). YopH dephosphorylates several proteins associated with the focal adhesion in eukaryotic cells, thereby enabling the bacterium to avoid phagocytosis and destruction by macrophages.

In collaboration with Terrence Burke Jr. (Laboratory of Medicinal Chemistry, CCR), we identified several tripeptide analogs that inhibit YopH with IC_{50} values in the low micromolar range. Thus far, we have managed to crystallize one of these compounds with the enzyme and solve the co-crystal structure at 2.2-Å resolution.

In addition, we determined a high-resolution structure (1.5 Å) of the YopH PTPase in complex with a nonhydrolyzable hexapeptide substrate analog, which promises to provide yet another starting point for the development of inhibitors.

Fran Pollner

Han Wen

Han Wen *received his Ph.D. in physics from the University of Maryland, College Park, in 1994 under the mentorship of Michael Fisher and Ralph Nossal of the University of Maryland and Robert Balaban of NIH. He joined the Laboratory of Cardiac Energetics, NHLBI, in 1995 and is currently a senior investigator in that lab.*

My research interest has always been the development of imaging technologies with potential applications in humans. In the early part of my NIH experience, I had the opportunity to work with a high-field MRI scanner.

The high magnetic resonance frequency, which is proportional to the field strength, yielded various interesting electromagnetic wave propagation phenomena in the body, including disruption of the uniformity of image sensitivity in the human chest.

With theoretical modeling and human scans at 1.5 tesla, 3 tesla, and 4 tesla, my colleagues and I showed that the optimal field strength for imaging the heart was around 2 tesla. I then continued to develop MRI techniques and in particular techniques for studying the biomechanics of the heart and vascular system.

One technique called DENSE (Displacement ENcoding with Stimulated Echo) is capable of mapping at high resolution the motion of the heart wall and the walls of major arteries, revealing the stress loading and compliance of the tissue in these areas. Such information is useful in diagnosing heart disease and in learning about the mechanical factors in atherosclerotic lesion formation and rupture.

A challenging problem in cardiac mechanics is how to map the muscle fiber structure of the heart noninvasively. My postdoc and I observed an interesting effect from a nanoparticle MRI contrast agent that is closely related to the capillary and fiber structure of the myocardium. We then discovered a simple and robust way to map the myofiber structure in vivo; it is based on the correlation between the image intensity and capillary orientation when the contrast agent is present.

My high magnetic field experience led to an interest in tissue electrical properties, which vary greatly among different types of tissue and therefore can provide great image contrast. I realized that in a high magnetic field an ultrasound pulse traveling in tissue should generate weak but detectable electrical signals, due to the Lorentz force on the charged molecules.

If the ultrasound is focused, as in ultrasonic imaging, then the electrical signal also forms an image that reveals electrical conduction properties of tissue. I called this Hall effect imaging and made devices that demonstrated 3-D imaging with this idea.

In the long term, I see many exciting ideas to be explored in the field of imaging. We all know that the human body is amenable to the propagation of several forms of energy waves, including ultrasound, radiofrequency electromagnetic, infrared and much higher frequency X-ray, and even gamma ray waves.

Biomedical imaging either relies on the interaction of these energy waves with tissue to provide image contrast or uses them to carry information out of the body to the detectors—and frequently both.

Contrast agents greatly widen the information content of the image and often lead to new imaging techniques. The recent progress in monochromatic X-ray sources opens new areas of X-ray imaging and contrast agent development. I hope to continue to explore new ideas and contribute to the growing capabilities of noninvasive imaging in biology and medicine. ■

Catalytic Reactions?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not **send it to us via e-mail: catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2E26.**

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

In Future Issues...

- Myopathy Genetics In the Middle East
- NCCAM Fellows Find Varied Homes
- OBSSR Turns 10

Kid's Catalyst: Shadow Casting

Overhead projectors aren't just for those wonderful (Wake up!) class room presentations. The next time you're waiting for your teacher to set up a lesson, you might want to do a little side experiment of your own.

Few can resist making shadows of different shapes with their hands when they see a blank screen. (Adults want to. They just don't most of the time.) If you're sitting in the front of the class, further away from the projector, the shadow you cast is much smaller than that of someone in the back, who is much closer to the light source. Your little shadow doesn't have a chance!

How much larger is the shadow of the classmate sitting behind you? Two rows back? Three rows back? How much does the size of the classmate matter? We're going to find out. Here's what you'll need:

1) A projector or another focused light source—such as a flashlight

2) Round objects. I happened to have a baseball, a golf ball, and a basketball lying around, but if you don't have similar props, you can create round disks of different sizes with your compass (homemade or otherwise . . . . remember how to do that?) and can tape them to a ruler or a pencil

3) A piece of paper taped to the wall the shadow will be cast on (and a volunteer to trace the shadow that will be cast)

4) Measuring tape

First, measure from the wall to the light source. With one person holding the golf ball and one person holding the baseball, make their shadows the same size. How far away do they have to be from each other in order to cast shadows of the same size?

The golf ball is much smaller than the baseball, but it can cast just as large a shadow when it's closer to the light source. But how much closer? Calculate the distance with your measurements on the floor, write them down, and then compare that with the diameter of the objects. Now try with different sizes. If one ball is twice as large as the other, does it need to be twice as far to create the same shadow?

Think of this experiment the next time you hear about an eclipse—when the sun blocks some or all of the moon, or vice versa—and how we can calculate the size and movement of an object based on its shadow dynamics. How much of a difference does a small change make in its shadow?

So now you need not fall asleep waiting for a presentation to start. Have fun playing with your own shadow!

—Jennifer White

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2E26, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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